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Is H&E morphology coming to an end?

H Fox

The title and subject of this contribution were inflicted upon me by the editors of this Journal and were not of my own choosing. The question posed to me by the title had never entered my mind, and my instinctive and intuitive response to it was "Of course H&E morphology is not coming to an end." However, every now and again one is forced to provide logical reasons for an intuitive belief and it is a useful exercise to consider both the present and future status of simple morphological diagnosis in histopathological practice.

When considering the future it is, however, necessary to point out that only those who are either extremely foolish or recklessly brave make short term predictions for the correctness of such prophecies will be proved or disproved within a brief time span, usually while the forecaster is still alive and hence still available to be ridiculed. Very long term predictions—for example extending over a millennium—are, however, free from such danger and can be made with a degree of abandon that allows even the most outré of prospects to be postulated without running the risk of future derision and scorn: this is because when the truth does eventually emerge both the forecaster and those to whom the forecast is made will be not only dead but long forgotten.

Any sensible forecaster is therefore going to take the short long-term future as their remit, thus avoiding both almost immediate retribution and long delayed irrelevance. As neither I, nor any other living person, can make any sensible predictions as to the future beyond the next 50 years I shall take that period as the blank canvas on which to paint (presumably in red and blue) my views on the possible demise of H&E morphology.

It is necessary first to consider the present state of diagnostic histopathology. It is commonplace, virtually platitudinous, to say that the practice of histopathology has changed almost beyond recognition during the last three or four decades. This is, however, largely untrue. It is correct that the scope of pathology has widened and that greater diagnostic accuracy can often be achieved, but in my present somewhat undistinguished employment as a locum histopathologist most of my work is qualitatively very similar to that which I undertook nearly 40 years ago as a trainee pathologist. In most diagnostic laboratories the bulk of the routine work still consists, as it did four decades ago, of examining H&E stained sections. What has changed dramatically is the increased number of biopsies received, this increase being "consumer led" and attributable largely to the introduction of new clinical techniques such as endoscopy and colposcopy.

The persistence and continuing viability and growth of H&E morphology indicates that this simple technique continues to meet most of the requirements of not only pathologists but also clinicians and, let us not forget, patients. This is all the more remarkable because the death knoll of simple microscopic morphological diagnosis has been sounded on many occasions during the last half century. At the time of my entry into the discipline of diagnostic pathology it was the perceived wisdom that the future lay with electron microscopy, a technique that gave the pathologist an unrivalled opportunity to study lesions at a truly cellular and subcellular level. Pathology departments invested heavily in expensive electron microscopes, electron microscopic preparation rooms were set up, and junior pathologists were expected to undertake extensive training in this exquisite tool which was going to revolutionise both diagnostic work and research. The ascendancy of electron microscopy as a diagnostic tool was, however, short lived and after only a few years it went into rapid and apparently irreversible decline. Today electron microscopy still has a niche and still has its eloquent advocates[1 2]; nevertheless electron microscopes have virtually vanished from most diagnostic laboratories and these expensive pieces of equipment largely lie gently gathering dust, being awakened from their slumber only by the occasional needs of neuropathologists and renal pathologists.

The next contender to enter the field and challenge the supremacy of H&E morphology was immunohistochemistry. The passage of time has now allowed the initial hyperenthusiasm with which this technique was originally greeted to subside sufficiently for it to appear in its true guise. This is as an important accessory technique which in most areas of histopathology is only relatively rarely required to make a primary diagnosis, its most significant applications being in the diagnosis of poorly differentiated neoplasms and in the categorisation of lymphomas. This view may not be palatable to all but it has been my experience when dealing with a considerable amount of referred material that if I was not able to make a diagnosis on H&E sections it was only very rarely that diagnostic clarification was achieved by immunocytochemistry. It remains true, of course, that immunohistochemistry is often important in the confirmation of a diagnosis, but it cannot be seen as a genuine usurper of H&E morphology.

Currently molecular and genetic techniques hold unrivalled sway in research laboratories and are vastly increasing our understanding of the basic biology of disease. Are they, however, percolating through to routine diagnostic laboratories and is there, in fact, any necessity or

Department of Pathological Sciences, Stopford Building, University of Manchester, Manchester M13 9PT, UK
H Fox

Correspondence to:
Professor Fox.

call for them to do so? The research value of these techniques is beyond doubt, but their current diagnostic value is limited, their outstanding successes being the rapid identification of infective agents by the polymerase chain reaction and the diagnostic classification of leukaemias and some soft tissue and paediatric tumours. Otherwise the application of molecular and genetic techniques in the field of oncology yields little that is currently of clinical importance to the oncologist or surgeon. Factors such as gene rearrangements, cytogenetic abnormalities, expression of tumour suppressor genes, oncogene expression, and apoptotic indices are of great theoretical interest but do not currently offer any information that would lead clinicians treating the common solid tumours to alter their therapeutic approach to any individual case of neoplastic disease.

It is clear therefore that at the present time H&E morphology retains a tenacious hold upon the discipline of diagnostic pathology. Will it, however, continue to do so in the future? Any consideration as to the future of pathology can not be made in isolation from changes in other branches in medicine and from changes in the patterns of disease. It is perfectly possible to envisage that some, or even many, non-neoplastic diseases will succumb to medical advances during the next 50 years while, by contrast, there is a near certainty that the incidence of cancer will increase and that this disease, which already occupies an important role in pathological practice, will become pivotal to the future of diagnostic pathology. The rise in cancer incidence will be entirely a result of increased longevity of the population but there may be, will be, some who argue that many cancers are potentially preventable, and that a combination of "healthy" living and preventive medicine will reduce the incidence of cancer. If a *soi disant* healthy lifestyle does in fact prevent premature death, often from cardiovascular disease, and increase longevity this will simply result in an increased incidence of cancer, as it will allow a greater percentage of the population to become elderly. Several forms of cancer are obviously susceptible to preventive measures but prevention of one form of cancer seems only to result in an increased incidence of another, and overall the incidence of cancer continues inexorably to rise not only in this country but all over the world. Nobody has shown that it is possible now to reduce the overall incidence of cancer, and only the most incurable optimist can seriously believes that this will become possible in the next 50 years.

I take as my central thesis, therefore, that the future of histopathology is inextricably linked with cancer and I doubt if the pathologist will cease to play a central role in this disease. It could be argued that increasingly sophisticated imaging and analytical techniques will usurp the pathologist's star role in the diagnosis of cancer, though previous claims that new imaging techniques, such as computed tomography and nuclear magnetic resonance, would obviate the need for most biopsies and render the presence of pathologists superfluous have proved to be illusory. Nevertheless I would freely grant that increasingly sophisticated imaging techniques may come to play a primary role in diagnosing the presence of a neoplasm. The mere fact that a tumour is present is, however, only the initial step in the management of a patient with cancer and I do not think that non-morphological techniques will be capable of assessing factors such as histological type, mitotic counts, and histological grade which, despite the plethora of other proposed prognostic indices, remain as the paramount prognostic indices always emerging as such in multivariate analyses. Indeed, in the whole of that aspect of pathology with which I have been most concerned the only new technique which has proved to be of sufficient prognostic value to merit inclusion in tumour treatment protocols has been the use of flow cytometry in endometrial adenocarcinoma.

Hence, while the current therapeutic approach to cancer persists, so will the dependence on H&E morphology. That there will be changes in cancer therapy over the next 50 years is certain but how radical will they be and will they obviate the need for H&E morphology? It is worth noting that there has been no significant change in our methods of treating cancer since the introduction of chemotherapy half a century ago. The aim is still that of either removing or killing all the malignant cells by various permutations of surgery, chemotherapy, and radiotherapy. This is, as some of the more realistic oncologists will accept, a crude and often ineffective approach which can be refined and fine tuned but from which no truly major reversal of death rates from cancer can be expected. The pressing question at the moment, therefore, is whether or not gene therapy holds out a true ray of hope, for if this form of management becomes widely used it is probable that the practice of pathology will have to change and that molecular and genetic techniques will have to become incorporated into routine histopathology.[3] The possibility that gene therapy may become a realistic proposition has generated numerous research grants, PhDs, promotions, overseas meetings, chairs, and publications but, apart from the benefits that have accrued to research workers, has generated very little of real clinical value. Indeed, the high hopes of a few years ago have tended to diminish or even evaporate, an attitude summed up most eloquently by James Le Fanu in his recent (and essential to read) account of *The Rise and Fall of Modern Medicine*[4]: "The new genetics begins to appear like a relentless catalogue of faded aspirations. This discrepancy between the perceived and the actual achievements of the new genetics is pivotal to any analysis of the current state of medicine."

Many will claim that this is a premature judgement and that it will be at least another decade before the true value, or even the presumed triumphs, of gene therapy will be apparent.[5] My guess is, however, that Le Fanu is right and I think that any success eventually achieved by gene therapy within the current context of the treatment of cancer will be mod-

est and restricted and that it will come to acquire a specific niche, rather as the once much vaunted interferon has found its outstanding role to be in the treatment of hairy cell leukaemia.

The notable heterogeneity of the cells in any single neoplasm is perhaps the strongest argument against major success being achieved with gene therapy in the present ethos of cancer management, and remains the strongest argument for the present "remove or kill" approach. I think it probable, however, that during the next 50 years attention will turn away from "curing" cancer towards making it a disease with which the patient can live symbiotically without any major impairment of their health, in much the same way as do women who coexist for decades with metastatic endometrial stromal sarcoma without any obvious discomfort. This may be achieved by altering the nature of the neoplastic cells so that their rate of growth is slowed or by obliterating their metastatic potential: methods of achieving this aim include, but are not restricted to, gene therapy and, if they are to be effective and widely used, will almost certainly have to be independent of the specific genetic or molecular characteristics of the neoplastic cells: I say this because I don't think that even with the passage of 50 years we will have either the technology or the financial means to treat each neoplasm on an individual basis. Hence even if the use of molecular and genetic techniques eventually becomes more widespread in diagnostic histopathology, the bed rock of pathological diagnosis will, for the foreseeable future, remain the H&E stained section.

This is not to say, however, that these H&E sections will be looked at in exactly the same way as they are today. It is now quite clear that image analysis systems can extract much more information from a stained section than can the naked eye, and I think that most H&E stained slides will eventually be read, and diagnosed, from a computerised automatic image analysis scanning system. Such a system will have built into it a complete databank and reference system that will enable it not only to read off a diagnosis but also, in difficult cases, provide a differential diagnosis, with an odds estimate for each possibility. The system will also, when necessary, provide a whole range of morphometric variables that are of prognostic value, performing this task in a consistent and objective manner.

My conclusion that we will still be employing, and indeed basically relying upon, H&E morphology in 50 years time will no doubt lead to accusations of my being complacent, outdated, reactionary, and well past it. I make, no apologies, however, for sounding a note of scepticism, or possibly realism, for, as Edmund Burke pointed out over 200 years ago, "to conceive extravagant hopes of the future is a common disposition of the greatest part of mankind."

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3 Quirke P, Mapstone N. The new biology: histopathology. *Lancet* 1999;**354**(suppl 1):26–31.
4 Le Fanu J. *The rise and fall of modern medicine.* London: Little, Brown and Co, 1999.
5 Smith AE. Gene therapy—where are we? *Lancet* 1999; **354**(suppl 1):1–4.